REMARKS

Reconsideration is respectfully requested.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Status of Claims

Applicants respectfully thank the Examiner for noting the election of species.

The Examiner states that claims 16, 28, 30-31, 41, 47-51 53, 79 and 80 are withdrawn as directed to a non-elected invention. Claims 16, 28, 41 and 53 are directed to the elected species 239D. Claims 30, 31 79 and 80 are directed to the elected species "increased affinity for FcγR." Claim 47 is directed to the elected species "aglycosylated Fc" and "position 239." Claims 47-51 and 53 are directed to the elected species aglycolylated and position 239. New claims 86 and 87 have been added.

As claims 16, 28, 30-31, 41, 47-51 53, 79 and 80 are directed to elected species, Applicants respectfully request that they not be withdrawn.

Claims 1, 2, 4-38, 40-51, 53-55, 57-59 and 61-85 are currently pending. Claims 3, 39, 52, 56 and 60, have been cancelled. Claims 1, 2, 4-8, 12-14, 18, 26, 32-34, 40, 43, 47, 55, 61, 62-66, 69, and 82-85 have been amended.

The positions of claim 3 have been incorporated into claim 1. The positions of claim 39 have been incorporated into claim 34. The positions of claim 52 have been incorporated into claim 47.

Priority

The Examiner asserts that the priority documents fail to provide support for position 239.

Applicants respectfully traverse this observation of the Examiner. Because the Examiner does not cite any art with a critical date falling between the claimed priority date and the filing date of the instant application, this observation remains moot.

Information Disclosure Statement

The Examiner states that certain references have been considered only to the extent that the abstracts are in English.

Applicants note that the abstract of the cited references is a "concise explanation" as required by M.P.E.P. § 609.04(a) III for purposes of information disclosure requirements.

35 U.S.C. §112, second paragraph

The Examiner has rejected numerous claims as indefinite under 35 U.S.C. §112, second paragraph on multiple grounds.

A. "modulate"

The examiner has rejected claims 1, 3, 6, 7, 10, 11, 18-27, 34, 35 and 59 as indefinite over the term "modulate."

Without acquiescing to the Examiner's rejection, Applicants have amended the claims to recite an Fc variant that "increases binding affinity to an FcγR as compared to said parent polypeptide" to conform with the species election.

This ground for rejection is therefore moot. Applicants respectfully request that it be withdrawn.

B. Claim 34: "effector functions"

The Examiner rejects claim 34 as indefinite over the recitation of the term "effector function."

Without acquiescing or admitting to the Examiner's position, Applicants have amended claim 34 to recite "ADCC or ADCP" as suggested by the Examiner.

This ground for rejection is now moot. Applicants respectfully request that this ground for rejection be withdrawn.

C. Claims 6, 12, 13, 18 and 43: "substantially human," "substantially mouse, substantially rat, substantially monkey"

The Examiner has rejected the terms "substantially human," "substantially mouse," "substantially rat" and "substantially monkey" as indefinite. Without acquiescing to the Examiner's rejection or admitting to the Examiner's position, Applicants have amended the claims to delete the term "substantially."

This ground for rejection is rendered moot. Applicants respectfully request that the present ground for rejection be withdrawn.

D. Claims 23-27: FcγRIIIa-fold:FcγIIb-fold

The Examiner has rejected claims 23-27 over the term FcγRIIIa-fold:FcγIIb-fold. The Examiner states that the phrase "is not defined by the claims, [and] the specification does not provide [a] standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention."

In claim 23, which depends from claim 1, the FcγRIIIa-fold:FcγIIb-fold ratio refers to a way of comparing the increase in binding of the claimed Fc variant to the FcγRIIIa receptor to the increase in binding of the variant to the :FcγIIb. Applicants have fully described this concept in Example 3 in paragraphs 211 and 212. The fold ratio refers to the ratio of "A" to "B" (e.g. A:B), where "A" is the x-fold increase in binding of the Fc variant to FcγRIIIa and "B" is the x-fold increase in binding of the Fc variant to FcγIIb.

By way of example and not limitation, Table 61 refers to a number of specific modifications having a FcγRIIIa-fold:FcγIIb-fold ratio. Variant 209 (the substitutions S239D/A330L/I332E) has an "FcγRIIIa-fold" value of 138.63. The Fc variant thus has a 138.63 fold increase in binding to FcγRIIIa over the parent Fc protein. Variant 209 also has an "FcγIIb-fold" value of 7.50. The Fc variant thus has a 7.50 increase in binding FcγIIb as compared to the parent Fc variant. The ratio of the 138.63 fold increase of binding to FcγRIIIa to the 7.50 fold increase in binding to FcγIIb yields a FcγRIIIa-fold:FcγIIb-fold ratio of 18.48.

The specification further provides data supporting the fold ratio. For example, the specificity profile defined by this ratio is shown in Figures 16a and 16b. Table 61 shows the fold enhancement of different FcγR effectors. Based on the disclosure provided in the specification, one of skill in the art would readily ascertain the meaning of FcγRIIIa-fold:FcγIIb-fold ratio.

Applicants respectfully request that in light of the foregoing, the claims are neither vague nor indefinite. This ground for rejection should be withdrawn.

35 U.S.C. §112, first paragraph - Enablement

Claims 1-3, 6, 7, 10-15, 18-27, 34-40, 43 and 59 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement requirement.

The Examiner rejects the phrase "a polypeptide comprising an Fc variant."

Without acquiescing to the propriety of the rejection, the claims have been amended to recite specific substitution positions within the Fc variant. In addition, the Examiner suggests that amending the claims to antibody and/or immunadhesin would obviate this ground for rejection. The Applicants respectfully draw the Examiner's attention to new claims 86 and 87, which recite "antibody" and "Fc fusion". For clarification, "fc fusions" are defined at paragraph [083] as

> a protein wherein one or more polypeptides is operably linked to Fc. Fc fusion is herein meant to be synonymous with the terms "immunoadhesin", "Ig fusion", "Ig chimera", and "receptor globulin" (sometimes with dashes).

Accordingly, the Applicants submit that the specification fully enables the claimed invention and the rejection should be withdrawn.

Rejection under 35 U.S.C. §1112 first paragraph - Written Description

The Examiner has rejected claims 1-3, 6, 7, 10-15, 18-27, 34-40, 43 and 59 under 35 U.S.C. §1112 first paragraph as lacking a written description.

The Examiner states that Applicants provide and "insufficient written description in the specification as-filed of 'a polypeptide comprising an Fc variant.'" (Emphasis Examiner's). The Examiner further asserts that the applicants have not provided "a 'representative number of species'." (Emphasis Examiner's). Applicants respectfully traverse this ground for rejection. However, in the interests of furthering the prosecution of this case, and without acquiescing to the propriety of the rejection, the claims have been amended to recite specific positions for amino acid substitutions. As such, the Applicants submit the written description is sufficient, and the rejection should be withdrawn.

Rejections under 35 U.S.C. §102(b)

Claims 1-3, 6, 7, 10-15, 18-27, 34-40, 43, 59 and 63 stand rejected over Presta WO 00/42072.

The Examiner asserts that Presta teaches a polypeptide comprising a variant Fc region. The Examiner further argues Presta teaches the Fc region can be modified by amino acid substitutions at positions such as 239, and cites the Summary of the invention at pages 5-8 for support. The Examiner further argues that Presta teaches that an "amino acid substitution can be a replacement of any naturally occurring amino acid residues e.g. Asp (D)," pointing to pages 14-15. The Examiner concludes that "the functional limitations associated with the peptide variant would be inherent properties of the reference antibody."

Anticipation requires that every limitation of the claim in issue be disclosed, either expressly or inherently, in a single prior art reference. *In re Paulsen*, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); M.P.E.P. § 2131 (citing *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Presta fails to anticipate the claimed invention for the reasons stated below.

A. With respect to claims to at least one substitution at the elected position 239, Presta fails to anticipate an Fc variant comprising "at least one substitution at ...position ...239, ...wherein said Fc variant increases binding affinity to an FcγR as compared to said parent polypeptide."

The polypeptide of claim 1 comprises an Fc variant that has both a structural and functional limitation. Specifically, the Fc variant must a) include at least one substitution at the elected position 239, and b) the Fc variant must have "increased binding affinity to an FcγR as compared to [the] parent polypeptide." A substitution must meet both the structural and functional claim limitations to be within the scope of the claimed invention.

Presta does not teach the claimed species position 239 having the required functional limitation. At page 5, line 32, Presta discloses that a group of modifications that include elected position 239 display "reduced binding to an FcγR." At page 6, line 10, Presta discloses that a group of modifications that include position 239 display "reduced binding to an FcγRIIIa." The best demonstration of this is in Table 6, which discloses the sole substitution at position 239, which was an alanine substitution, 239A. Table 6 shows that 239A has reduced binding affinity to both FcγRIII and FcγRII. Amino acid substitutions that do not result in an Fc variant with increased binding affinity to an FcγR are outside the scope of claim 1. Without meeting the positive functional limitation, Presta cannot anticipate the claim.

The claimed polypeptide is also not inherent in the teaching of Presta. To be inherent, the claimed limitation must "necessarily flow" from the teachings of the cited reference. The mere fact that a claimed compound may have the claimed function is insufficient to establish inherent anticipation. See M.P.E.P. § 2163.07(a). As noted above, page 5, line 32 of Presta discloses that modifications at position 239 display "reduced binding to an FcγR," page 6, line 10 of Presta discloses that modifications at position 239 display "reduced binding to an FcγRIIIa", and Table 6 shows the sole 239 variant, 239A, has decreased binding to both FcγRIII and FcγRII. One of skill in the art would not draw the conclusion that variants at position 239 would "necessarily" result in increased binding; rather, if anything, the opposite inference could be drawn.

Further, Presta does not disclose any specific substitution at position 239 that inherently has the claimed functional limitation. As discussed below, Presta provides a generalized teaching for making modifications at a large genus of numerous positions in the Fc region. In this context, such a generalized teaching of a genus is not an anticipatory teaching of a specific substitution at a specific position. As such, Presta does not teach any substitution at the elected position 239 that inherently "increases binding affinity to an FcγR" as claimed.

B. With respect to claims to the elected substitution 239D, Presta's disclosure of position 239 and the separate teaching that amino acids can be substituted do not anticipate the elected substitution species 239D.

The courts have clearly held that broad, generic formulas or descriptions of a large class of compounds, in the absence specifically naming a species or providing a much more limited subset of

specified preferences for *particular* compounds that encompasses the claimed species, are not sufficient to support an anticipation rejection. Accordingly, Applicants submit that the issue at hand is whether 1) the published Presta PCT has clearly named the elected species 239D sufficient to anticipate the claimed invention, or 2) the published Presta PCT has merely provided a broad generic disclosure representing a vast number of positions that do not unequivocally disclose the substitution 239D or direct those skilled in the art to the compound without any need for picking, choosing, and combining various separate disclosures within a single reference.

1. Presta does not anticipate the claims because it does not specifically describe the claimed species 239D.

The Examiner cites *Ex parte A* in support of the 102(b) rejection over Presta. *Ex parte A* is directed to circumstances in which the prior art specifically and distinctly names a specific compound. As the Examiner notes, the Board held that

> [t]he tenth edition of the Merck Index lists ten thousand compounds. In our view, each and every one of those compounds is 'described,' as that term is used in *35 USC 102*(a), in that publication."
> *Ex parte A*.

The Board clearly drew a correlation with a reference manual (the Merck Index) where each compound listed in that reference is specifically and separately named. In other words, in the Merck Index, each monograph in the encyclopedia discusses a single chemical entity or a small group of very closely-related compounds, such that one could compare one compound to another on a direct, one-to-one basis.

The Examiner also cites *In re Sivaramakrishnan*, 673 F.2d 1383, 213 USPQ 441 (CCPA 1982) in support of the novelty rejection. Like *Ex parte A*, *In re Sivaramakrishnan* concerned a prior art disclosure that specifically and separately named a claimed compound (i.e. cadmium laurate) in a list of specifically and separately named compounds. The *Sivaramakrishnan* court held that the cited reference anticipated the claimed compound because the compound was specifically and separately named in the prior art reference. The *Sivaramakrishnan* court further held that unexpected advantages of the disclosed compound were irrelevant to the determination of novelty.

The factual circumstances of the prior art references in *Ex parte A* and *In re Sivaramakrishnan* differ fundamentally from those of Presta as applied to the presently elected species 239D. Unlike the references of *Ex parte A* and *In re Sivaramakrishnan*, Presta fails to separately and clearly name an Fc variant comprising 239D from among the large number of disclosed substitutions. In Table 6, Presta specifically and separately names an Fc region having the substitution 239A, but not the elected substitution 239D. Presta never expressly discloses 239D. As such, the species 239D is not anticipated like the compounds specifically named in *Ex parte A* and *In re Sivaramakrishnan*.

2. One of skill in the art would not "at once envisage" the claimed species 239D from the disclosure of Presta.

Applying Presta to the presently elected species 239D is instead analogous to the factual circumstances of *In re Petering,* 301 F.2d.676, (CCPA 1962), *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978) and *In re Arkley*, 455 F.2d 586, 172 USPQ 524 (CCPA 1972), which are disclosed in M.P.E.P. §§ 2131.02 and 2144.08.

In re Petering concerned a prior art disclosure that included both a broad generic formula representing a vast number of compounds (i.e. a genus), and a "much more limited list" of certain "specific preferences" of about 20 specific compounds (i.e. a subgenus). The disclosed subgenus was directed to a generic formula for isoalloxazine compounds, and recited that variable substituents X, Y, Z, P and R' were either hydrogen or alkyl radicals, and R a side chain containing an OH group. The *Petering* court stated that "[e]ven though appellants' claimed compounds are encompassed by [the] broad generic disclosure, we do not think this disclosure by itself describes appellants' invention...within the meaning of 35 U.S.C. 102(b)."

The *Petering* court then held that a claimed compound was only anticipated by the prior art reference because the claimed compound could be "at once envisaged" from a separately identified subgenus of preferred substituents within the broad genus that encompassed twenty possible compounds. It was only a particular specific preference that defined the subgenus of the broad generic compound that was found to anticipate the claims.

Similarly, in *In re Schaumann*, a claim to a single compound was found to be anticipated by a prior art reference that contained both a generic formula and, as in *In re Petering*, the prior art reference had specified a preference for a particular subgenus of compounds that encompassed the claimed compound. The *Schaumann* court reiterated the requirement of *In re Petering* that the claimed compound must be at once envisaged from the cited reference. The *Schaumann* court further pointed to the decision in *In re Ruschig,* 52 CCPA 1238, 343 F.2d 965, 145 USPQ 274 (1965) in which the court held that broad generic disclosures in multiple references could not be recombined to support anticipation rejections. The court stated:

> "[w]e did not intend our *Petering* opinion or decision to become a precedent for the mechanistic dissection and recombination of the components of the specific illustrative compounds in every chemical reference containing them, to create hindsight anticipations with the guidance of an applicant's disclosures, on the theory that such reconstructed disclosures describe specific compounds within the meaning of section 102. Furthermore, we do not find the present case to be of the type we had before us in *Petering*. Even if we take the 10 examples of the French [first reference] or the 12 examples of the Swedish reference [a second reference], take them apart and recombine them into different compounds than those named, we do not get a small recognizable class with common properties.

In *In re Arkley*, 455 F.2d 586, 172 USPQ 524 (CCPA 1972), the court held that a generic class of compounds having a particular formula (conservatively containing over 230,000 compounds, including the appellant's compound) do not anticipate the appellant's claimed compound. In that *Arkley*, the court stated that:

> for the instant rejection under *35 USC 102*(e) to have been proper, the...reference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.

The *Arkley* court further stated that:

> there is nothing in the teachings relied upon by the Patent Office which clearly and unequivocally directs those skilled in the art to make this selection nor any indication that...[the prior art reference]...ever made the selection himself.

The courts have further held that disclosure of a broad genus in the absence of any teaching to a narrow genus of preferred compounds is not sufficient to anticipate a claim to a compound. In *Schering Corp. v. Precision-Cosmet Co.*, 614 F. Supp. 1368 (D. Del. 1985), a broad prior art disclosure of substituted styrenes did not anticipate a specifically claimed styrene species. With reference to a claimed specific substituted styrene having a particular property, the court stated that the prior art reference:

> does not mention any particular substituted styrene, makes no references to the permeability of specific substituted styrenes, and provides no basis whatever for preferring any sub-group of substitute styrenes over other substituted styrenes...Given the fact that substituted styrenes comprise a class in excess of one hundred compounds, it seems clear that the elements of the claimed invention...were not adequately described...for purposes of identification; and that one of ordinary skill in the art would have had to engage in extensive experimentation to get from [the prior art disclosure] to the [claimed] invention.

Schering Corp. v. Precision-Cosmet Co. also states that a genus does not anticipate unless preferred compounds are disclosed within that genus:

> The general rule is that a prior genus does not anticipate a later species. *Chisum, Patents §3.02*[2] (1985); *see In re Ruschig, 52 C.C.P.A. 1238, 343 F.2d 965 (C.C.P.A. 1965).* If, however, it is possible to derive a class of compounds of lesser scope than the genus disclosed in a prior art reference on the basis of preferences ascertainable from the remainder of the reference, anticipation may be found. *E.g., Application of Schaumann, 572 F.2d 312, 316 (C.C.P.A. 1978); In re Petering, 49 C.C.P.A. 993, 301 F.2d 676, 681 (C.C.P.A. 1962).*

In summary, "a prior art reference that discloses a genus still does not inherently disclose all species within that broad category." *Metabolite Labs.*, 370 F.3d at 1367 (Fed Cir. 2004). Specifically, a genus anticipates a species when the species can be "at once envisaged" from the disclosure of the genus. See *In re Schaumann*, 572 F.2d 312 (C.C.P.A. 1978); see also *In re Petering*, 301 F.2d 676 (C.C.P.A. 1962). To "at once envisage" the formula one of skill in the art must be able to draw the structural formula or write the name of the claimed compound from the prior art disclosure of a generic chemical structure. *Id.*

Taken against the established caselaw, the claimed 239D species would not be "at once envisaged" from the Presta disclosure. Presta discloses a broad genus of Fc modifications at each amino acid in the Fc region. Unlike the art cited in *In re Petering* and *In re Schaumann*, Presta simply does not

disclose a subgenus or a preferred list that includes the elected substitution 239D. Specifically, Presta discloses 66 possible modification sites in the Fc region, one of which is position 239. In a separate section of the specification, Presta provides a generalized disclosure of modifications and substitutions without correlation to the claimed substitutions. Presta defines an "amino acid modification" broadly as "a change in the amino acid sequence of a predetermined amino acid sequence. Exemplary modifications include an amino acid substitution, insertion and/or deletion." As discussed above, Presta further defines a "substitution" broadly as including naturally and non-naturally occurring amino acids. The substitutions and modifications are not disclosed to be specific to a single position, and do not disclose the elected species 239D. Further, Presta Table 1 provides generalized teachings of conserved amino acids, and would suggest that to replace the serine at position 239, the exemplified and preferred substitution is a threonine.

A listing of every position, and for each position, every conservative substitution known to those of skill in the art, followed by every non-conservative substitution known to those of skill in the art, or a list of nearly every possible N- or C-terminal fragment of a given sequence, is not a list of specified preferences for a particular sequence or subset of sequences. There are simply no specifically disclosed or exemplified sequences in Presta constitute a specific preference for the elected 239D species. Further, Presta discloses that modifications at position 239A has decreased binding to FcγR, and does not point to a preferred group of substitutions that increase binding to FcγR.

Applicants respectfully submit that the Examiner is arguing in favor of exactly what the court cautions against. The courts prohibit reading a large genus of compounds as anticipating a claimed species unless the species is precisely and specifically named (see *Ex parte A* and *In re Sivaramakrishnan*) or is one of a preferred list of compounds within the genus (see *In re Petering*). Unlike the facts of *Ex parte A* and *In re Sivaramakrishnan*, Presta does not expressly disclose the elected 239D species. Like *In re Petering,* Presta discloses a broad genus of compounds that the *Petering* court expressly states do not meet the standard for novelty. Unlike the art cited in *In re Petering* and *In re Schaumann*, Presta does not disclose a preferred group of amino acid substitutions that include 239D.

Therefore, Presta does not anticipate the claimed species. Applicants respectfully request that this ground for rejection be withdrawn and that the additional non-elected species be examined consistent with the election of species requirements.

Rejections under 35 U.S.C. §102(e)

Claims 1-3, 6, 7, 10-15, 18-27, 34-40, 43, 59 and 63 stand rejected over Presta II (U.S. Patent No. 6,737,056).

Presta II does not anticipate the claims for the reasons described above in the response to the rejection under 35 U.S.C. §102(b). First, Presta II neither expressly nor inherently teaches an Fc variant

comprising "at least on substitution at ...position ...239, wherein said Fc variant increases binding affinity to an FcγR as compared to [the] parent polypeptide." Second, Presta II fails to anticipate the elected substitution species 239D.

As such, the presently claimed invention is not anticipated by Presta II. Applicants respectfully request that this ground for rejection be withdrawn.

Conclusion

In light of the above amendments and remarks, Applicants believe that this case is now in condition for allowance. Early notification is respectfully requested. Should there be any remaining issues that remain unresolved, the Examiner is encouraged to telephone the undersigned.

Please direct further questions in connection with this Application to the undersigned at (415) 781-1989.

Respectfully submitted,

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Dated: Sept 7 2006

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